REMARKS

Claims 4-8, 11-12, 16-19 and 28-31 remain pending in the application following entry of the amendments. Without conceding to the Examiner's position and in the interests of Applicant's business aims, claims 9-10 and 20-22 have been cancelled and claims 11, 22, 28, and 29 amended. Support for the amendments are found in the original claims and throughout the specification, for example on page 24 (lines 3-8) and pages 29-37. Applicants specifically reserve the right to pursue the cancelled subject matter in a related application.

Claims 4-12, 16-22, and 28-31 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. In view of the amendments to the claims, Applicants direct the following discussion to use of adenoviral vectors. The Examiner acknowledges enablement is shown for *in vivo* administration of Ad-HO-1 for *liver transplantation* and *ex vivo* perfusion with Ad-HO-1 of organs in general, but contends that the disclosure is not enabled for extending life of organ transplants other than the liver by *in vivo* administration of Ad-HO-I. The weight of the evidence as a whole, however, sustains a different conclusion.

Applicants submitted in their reply of April 3, 2003 a declaration by inventor Dr. Suhasini Iyer regarding prolonging of *cardiac allograft* survival in *graft recipients* following *in vivo* administration of an adenoviral vector expressing heme oxygenase I (Ad-HO-I). The Examiner appears to have inadvertently bypassed this declaration (copies enclosed), and Applicants request reconsideration of the evidence presented therein:

> A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement.

See M.P.E.P. § 2164.05. Paragraph 6 of the declaration explains that administration of Ad HO-1 by (1) direct injection into the transplanted heart, (2) administration to the hind limb muscle, or (3) intravenous delivery (*i.e.*, tail vein) into the *graft recipient* prolonged *heart allograft* survival. In contrast to the Examiners' predictions about the detrimental effects of tissue tropism, intravenous or intramuscular systemic delivery at sites distant from the graft showed the longest extensions of graft survival. Prolonging of cardiac allograft survival occurs despite adsorption of virus by other tissues and dilution by body fluids. Thus, the adenoviral based constructs are capable of infecting sufficient number of cells and altering heme-oxygenase levels in organs other than the liver to provide the claimed therapeutic benefit. Based on the evidence as a whole, a person skilled in the art would find more than a

reasonable correlation between scope of enablement and breadth of the claimed subject matter. The evidence answers the concerns expressed by the Examiner, and supports Applicants' position that specific organ targeting is not a prerequisite to achieve extension of graft survival of various organ types by *in vivo* or *ex vivo* treatment with Ad-HO-I.

Moreover, the Examiner appears to have narrowly focused on "systemic *in vivo* administration" to reject the claimed subject matter. Limiting *in vivo* contacting to "systemic administration," however, excludes other *in vivo* delivery methods equally capable of achieving the claimed results. As discussed in Applicants' reply of April 3, 2003 (Paper# 15), the specification provides for localized delivery by (1) direct injection into the transplanted organ and (2) intravascular injection proximate to the transplant organ (see Specification on page 25, lines 13-14 and 18-19). Direct injection into the target organ would limit the effects of tissue tropism discussed by the Examiner and enhance infection of cells in the subject organ.

Although the Examiner apparently dismisses these techniques, efficacy of such focal delivery is supported by the reference of Miller et al., *FASEB J.* 9:190-199 (1995) cited by the Examiner, references provided by Applicants (see, *e.g.*, Exhibit E: Qin, L. et al, *Transplantation* 59:809-816 (1995), submitted April 3, 2003; see adenoviral vectors on Table 4), and in particular, by the Declaration of Dr. Suhasini Iyer. Thus, the capability of adenoviral vectors to infect a variety of cell types and efficiently express a transgene is amply supported by the evidence of record and the scientific literature. Consequently, no more than routine experimentation would be required by a skilled artisan knowledgeable in various *in vivo* delivery methods to determine a suitable *in vivo* delivery regimen effective in prolonging graft survival.

In view of the foregoing, Applicants submit that the claims are fully enabled. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

CONCLUSIONS

Applicants submit that the pending claims are in compliance with all the requirements of patentability, and early notification of such allowance is earnestly solicited. If the Examiner feels there are further unresolved issues or believes that prosecution of the above-

referenced application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 544-7015.

Respectfully submitted,

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